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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,902	01/25/2001	Reba Goodman	61545/JPW/RAD	5006

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/769,902	GOODMAN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the "Amendment in Response..." filed 6 December 2002 (Paper No. 13) in reply to the Non-Final Office Action mailed 3 July 2002 (Paper No. 10). Claims 1-12 were considered in Paper No. 10. Claims 1, 3, 6 and 9 were amended in Paper No. 13. Claims 1-12 are pending and under consideration.

Response to Amendment

Specification

Objection to the disclosure for informalities cited in Paper No. 10 is withdrawn in view of the amendments to the specification in Paper No. 13.

Double Patenting

Applicant's arguments of record in Paper No. 13 regarding the distinct subject matter encompassed by claims 1, 2, 5 and 8 relative to claims 9, 10, 11 and 12, respectively, are found persuasive.

Claim Rejections - 35 USC § 112

Claims 1-12 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for reasons of record and herein below under "Response to Arguments".

Rejection of claims 1-12 under 35 U.S.C. § 112, second paragraph, as indefinite for reasons of record in Paper No. 10 is withdrawn in view of the amendments to the claims in Paper No. 13.

Claim Rejections - 35 USC § 102

Rejection of claims 1-12 under 35 U.S.C. § 102(a) as anticipated by Lin *et al.* (2001) *J. Cell. Biochem* 81:143-148 is withdrawn in view of Exhibit E, made of record in Paper No. 13.

Rejection of claims 1, 5-8, 9, 11 and 12 under 35 U.S.C. § 102(b) as anticipated by Lin *et al.* (1994) *J. Cell. Biochem.* 54:281-288 is withdrawn in view of Applicant's arguments of record in Paper No. 13.

Claim Rejections - 35 USC § 103

Rejection of claims 1-4, 8-10 and 12 under 35 U.S.C. § 103(a) as unpatentable over Han *et al.* (1994) *J. Cell. Biochem.* 54:281-288 in vies of Lin *et al.* (1994) *J. Cell. Biochem.* 54:281-288 is withdrawn in view of Applicant's arguments of record in Paper No. 13.

Response to Arguments

Claim Rejections - 35 USC § 112

In response to the rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph, as lacking enablement for gene therapy, Applicant asserts that the articles cited by the Examiner to evidence the unpredictability of gene therapy are outdated and that at the time the instant

application was filed many advances had been made in *in vivo* gene therapy. Applicant further asserts that at the time of filing *in vivo* gene therapy was not unpredictable and cites Wang *et al.* (2000) *Mol. Ther.* 1:154-158, which teaches long-term correction of the bleeding disorder in hemophilia B dogs by injection of a recombinant adeno-associated virus vector encoding canine factor IX under the control of a liver-specific enhancer/promoter, to support this assertion.

These arguments have been fully considered but are not found persuasive because the teachings of Wang *et al.*, in the context of the general unpredictability of gene therapy described in the many articles cited in the previous office action, are not enabling for treatment using the instant method. In particular, as stated in the previous office action, "Verma *et al.* teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma *et al.* [(1997) *Nature* 389:239-242] page 240, column 2). Verma *et al.* further warns that, '...the search for such combinations is a case of trial and error for a given type of cell' (Verma *et al. supra*, bridging sentence of columns 2-3)" and "Jin *et al.* (1997, *Bioelectrochem Bioenerg.* Vol. 44, No. 1, pages 111-120) teach that the efficiency of induction is dependent on the type of cells and the source of cells exposed to the electromagnetic fields (page 112, bridging paragraph of the columns)". Given these teachings, which demonstrate the unpredictability of obtaining therapeutic levels of expression from any given promoter system and the unpredictability of expression obtained using electromagnetic induction in any given cell type, the skilled artisan would not predict a therapeutic effect resulting from a method comprising introducing electromagnetic response elements into a gene promoter and applying an

electromagnetic field based on the teachings of Wang *et al.*, which are specifically directed to expression of a therapeutic gene in liver cells using a liver-specific promoter enhancer.

Next, in response to the Examiner's assertion that one of the factors that the art teaches affect efficient gene delivery and sustained gene expression is anti-viral immune responses, Applicant cites Rux *et al.* (2000) *Mol. Ther.* 1:18-30 and argues that Rux teaches, "new modified adenoviral vectors have been made which overcome the problem of immune responses" (page 9). This argument is not persuasive because it mischaracterizes the teachings of Rux. Rux teaches the X-ray crystal structure of type 5 adenovirus hexon and identifies serotype specific epitopes within the hexon protein. Rux *et al.* concludes, "[t]he improved understanding of hexon should greatly facilitate the design of new hexon molecules to produce chimeric adenovirus vectors for use in gene therapy" (second full paragraph in the second column on page 19). The statements in Rux *et al.* regarding designing adenovirus vectors to evade immune responses are merely prophetic and far from overcome the problem of immune responses.

Regarding the Examiner's arguments as to the lack of adequate direction provided, Applicant asserts that the specification, coupled with the knowledge and level of skill of the art at the time of filing, does enable a method of gene regulation *in vivo* using electromagnetic response elements. Applicant cites Junkersdorf *et al.* (2000) *Bioelectromagnetics* 21 :100-106, which teaches the effects of electromagnetic fields in the presence of heat shock on the expression of a reporter gene in *C. elegans*, as evidence for *in vivo* expression enhanced by electromagnetic fields. This argument is not persuasive because the foundation of the Examiner's argument is the unpredictability of obtaining expression at therapeutic levels *in vivo.* The teachings of Junkersdorf *et al.* do not address the unpredictability of therapeutic expression of a

nucleic acid molecule. Applicant also again cites Wang *et al.* as evidence that *in vivo* gene expression can be stable and at a therapeutic level. However, for the reasons provided above, the teachings of Wang *et al.* are not enabling for the instant method, which is directed to therapeutic expression using promoter elements and methodology that is dramatically different from those taught by Wang *et al.*

In response to the Examiner's statements regarding the level of predictability in the art and amount of experimentation required to practice the invention, Applicant again relies on the teachings of Wang *et al.* and Junkersdorf *et al.* to support enablement for the claimed method of gene therapy. Applicant further argues, "it is known that gene therapy can be used to treat many different types of diseases. Therefore, the specification by mentioning gene therapy, inherently means that it is a method of treating any genetic disease, and therefore, there is not a lack of guidance concerning the treatment of any disease using the claimed method of the instant invention" (page 14). Regarding the cited art, the skilled artisan could not rely on the teachings therein to provide enablement for therapeutic gene expression using the instant claimed method for the reasons provided above. Regarding the statement that it is known that gene therapy can be used to treat many different types of diseases, the art of record indicates that, as of the filing date of the instant application, gene therapy was effective only in the treatment of hemophilia B in dogs. However, for reasons of record, the teachings of the instant application and prior art do not enable the ordinary skilled artisan to use the instant claimed method to treat even that condition. Although gene therapy could in theory be used to treat a wide range of diseases, the art of record shows that that potential has not as yet been realized and, for reasons of record, could not be

realized based on the teachings of the prior art and instant disclosure without engaging in undue experimentation. Therefore, the claims stand rejected under 35 U.S.C. § 112, first paragraph.

New Grounds for Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended claims 1 and 8 such that they are directed to a method comprises introducing electromagnetic response elements into a gene promoter in a mammal. To support the amendment, applicant points to page 4, lines 5-12 of the originally filed specification. There is, however, no recitation of "a mammal" in the specification and thus the limitation adds new matter. In Paper No. 13, page 15, Applicant argues that the amended claims are inherently supported by the term "gene therapy" based on the American Society of Gene Therapy (page 15). However, the definition provided does not state that gene therapy is limited to mammals and thus does not support the added limitation.

Applicant's argument that introducing a construct into an animal is inherent to any method of gene therapy is persuasive, however, and rejection of the claims on the grounds that

the lack of an explicitly stated step of introducing the constructs into an animal renders the claims indefinite is withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in their recitation of "introducing electromagnetic field response elements into a gene promoter...in a mammal". The claim reads as though the electromagnetic field response elements are introduced into a promoter *in vivo*. The disclosure suggests, however, that the electromagnetic field response elements are to be introduced into a promoter *in vitro,* and it is the engineered construct that is then introduced into the animal. Applicant should amend the claim such that the order of the process steps is clearly set forth.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
February 20, 2003

JAMES KETTER
PRIMARY EXAMINER